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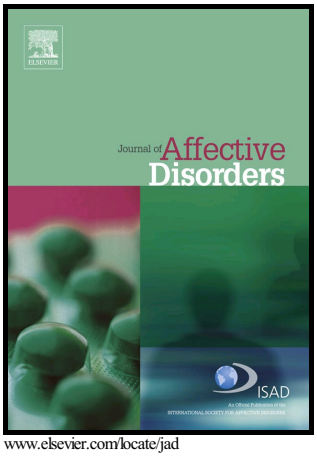

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A comparative meta-analysis of TEMPS scores across mood disorder patients, their first-degree relatives, healthy controls, and other psychiatric disorders

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Abstract

Background

The Temperament Evaluation Memphis, Pisa, Paris and San Diego Auto-questionnaire (TEMPS) is validated to assess temperament in clinical and non-clinical samples. Scores vary across bipolar disorder (BD), major depressive disorder (MDD), attention-deficit/hyperactivity disorder (ADHD),

borderline personality disorder (BPD) and healthy controls (HCs), but a meta-analysis is missing.

Methods

Meta-analysis of studies comparing TEMPS scores in patients with mood disorders or their first-degree relatives to each other, or to a psychiatric control group or HCs.

Results

Twenty-six studies were meta-analyzed with patients with BD (n=2,025), MDD (n=1283), ADHD (n=56) and BPD (n=43), relatives of BD (n=436), and HCs (n=1757). Cyclothymic ($p<0.001$) and irritable TEMPS scores ($p<0.001$) were higher in BD than MDD (studies=12), and in MDD vs HCs (studies=8). Cyclothymic ($p<0.001$), irritable ($p<0.001$) and anxious ($p=0.03$) scores were higher in BD than their relatives, who, had higher scores than HCs. No significant differences emerged between ADHD and BD (studies=3);

Conclusion

Affective temperaments are on a continuum, with increasing scores ranging from HCs through MDD to BD regarding cyclothymic and irritable temperament, from MDD through BD to HC regarding hyperthymic temperament, and from HC through BD relatives to BD regarding cyclothymic, irritable and anxious temperament. Depressive and anxious temperaments did not differ between BD and MDD, being nonetheless the lowest in HCs. BD did not differ from ADHD in any investigated TEMPS domain.

Limitations

different TEMPS versions, few studies comparing BD with ADHD or BPD, no correlation with other questionnaires.

Keywords: Affective temperament; Temperament Evaluation Memphis; Pisa; Paris and San Diego Auto-questionnaire; 110 item version (TEMPS-A-110); TEMPS; Major depression: bipolar disorder.

1. Introduction

The "Temperament Evaluation of the Memphis, Pisa, Paris, and San Diego" (TEMPS) has been extensively validated to evaluate sub-affective trait expressions as they were conceptualized in Ancient Greek psychological medicine and, in more recent times, by Nineteenth Century German psychiatry (Akiskal and Akiskal 2007, Rihmer, Akiskal et al. 2010).

The TEMPS has been developed based on the "Interview" version (TEMPS-I) released in the late 1990s (Akiskal, Placidi et al. 1998, Placidi, Signoretta et al. 1998), which was subsequently extended to include 84 items (Akiskal and Akiskal 2005), and ultimately leading to the current 110-item version of the TEMPS-A (Akiskal and Akiskal 2005, Akiskal, Akiskal et al. 2005). The TEMPS-A includes five domains and items, which serve as criteria for the cyclothymic, dysthymic, irritable, hyperthymic and anxious temperaments (Akiskal and Mallya 1987, Cassano, Akiskal et al. 1992). The TEMPS-A characterizes the dominant temperament of a subject, which results in a frequency of each temperament within a given population (e.g., about 10% of BP-II patients have cyclothymic temperament vs. 1% of healthy individuals (Mechri, Kerkeni et al. 2011)).

The TEMPS-A has been validated for use in both healthy people and those with a psychiatric diagnosis, in several languages and different settings, and has consistently demonstrated acceptable psychometric properties (Akiskal and Mallya 1987, Akiskal, Placidi et al. 1998). The theoretical construct of the TEMPS-A refers to a constitutional, genetically-determined, biological personality substrate of the individual reflecting an "endophenotype" trait that is stable across the lifespan (Nuttin 1985). Though void of any intrinsic psychopathological predictive value (Rutter 1987), the predominant affective temperament holds a place in the multifactorial model of mood disorders, mapping onto the subclinical extreme of the continuum that encompasses bipolar disorder type I (BD-I), type-II BD (BD-II), and major depressive disorder (MDD) on the opposite pole, including also other mood disorders not yet officially accepted (BD-III, IV) (Akiskal, Akiskal et al. 2006) or, possibly, the affective core of distinct diagnostic entities, such as borderline personality disorder (BDP) (Perugi, Fornaro et al. 2011) or, even, attention-deficit/hyperactivity disorder (ADHD) (Landaas, Halmoy et al. 2012, Ekinci, Ozdel et al. 2013).

From this perspective, varying combinations of affective temperamental domains could represent vulnerability markers to different disorders, especially cyclothymic temperament for BD-II or hyperthymic temperament for euphoric mania BD-I (Perugi, Maremmani et al. 2001), and could help differential diagnosis among mood disorders (Perugi, Toni et al. 2012). Nonetheless, although stable across the lifespan (Kawamura, Akiyama et al. 2010) and highly genetically-determined (Gonda, Rihmer et al. 2006) even in "affected or unaffected" first-degree relatives (Vazquez, Kahn et al. 2008), it is unclear whether the actual continuum proposed for affective temperaments across varying psychopathological and non-psychopathological conditions might be actually reflected by a progressive severity of scores.

To the best of our knowledge, no meta-analysis exists evaluating the TEMPS scores across patients with BD or MDD, patients with different psychiatric diagnoses, BD relatives and HCs. The present paper aimed to address this gap and provide the first quantitate report investigating the existence of a metric continuum of the different scores of the five essential domains of the TEMPS.

METHODS

The present meta-analysis adhered to the MOOSE guidelines (Stroup, Berlin et al. 2000) and PRISMA statement (Moher, Shamseer et al. 2015), following a predetermined, but unpublished protocol.

Search strategy and study selection

Two authors (MS, LZ) independently searched Scopus and PubMed from inception until August 1st, 2015 using the search terms ("temperament"[All Fields] OR "character"[All Fields]) AND ("depression" OR "major depression" OR "depressive disorder" OR "affective disorder" OR "bipolar disorder" OR "bipolar" OR mania OR "mood disorder"). The reference list of included articles and of recent reviews were checked for potentially eligible studies. Studies eligible for inclusion provided the following: i) administration of the TEMPS (any validated version) to patients with either BD or MDD or their first-degree relatives compared to each other or compared to ii) healthy controls (HCs); iii) other psychiatric disorders.

Data extraction

Two authors (MS, LZ) independently extracted data using a data extraction form, including: author, publication year , country, setting, demographic characteristics for BD and control groups (age, number of males, sample size), mean and SD of TEMPS scores in each group. When we identified an article that was eligible but did not contain sufficient data to enable inclusion in the meta-analysis, we contacted the corresponding authors up to three times over a month to request the data.

Outcome measures and quality assessment

The primary outcome measure was the study-based standardized mean difference (SMD) of each TEMPS score between patients with BD, MDD or their first-degree relative and each available control group. The study quality was independently assessed by two authors (LZ and MS) using a modified version of the Newcastle Ottawa Scale (NOS) (Wells, Shea et al. 2000). Our version of the scale was modified (NOS-M) (see Supplementary Material 1) to produce a score ranging from 0 (lowest quality) to 18 (highest quality), which was determined for each study by consensus between the two investigators.

Meta-analytic method

The meta-analysis was conducted in the following steps. First, we calculated the SMD statistic together with 95% confidence interval (CI) to establish the difference in each TEMPS affective temperament domain score, between patients with BD or MDD or their first-degree relatives and control groups, with RevMan (Review Manager, v5.2) (RevMan). Second, we conducted meta-regression analyses with Comprehensive meta-analysis (CMA, version 3, http://www.meta-analysis.com) (CMA)to investigate the following moderators: sex, phase of the disease in both BD and MDD, country of origin. Heterogeneity was assessed with I^2 statistics for each analysis, with a value of $\geq$50% indicating high heterogeneity (Higgins, Thompson et al. 2003). Publication bias was assessed with a visual inspection of funnel plots and with the Begg-Mazumdar Kendall's tau (Begg and Mazumdar 1994) and Egger bias test (Egger, Davey Smith et al. 1997). In case of significant findings indicating publication bias, we calculated the trim and fill adjusted analysis (Duval and Tweedie 2000) in order to evaluate if the results changed after imputing potentially missing studies.

RESULTS

Selection of studies and retrieved sample

The study selection process is shown in Figure1. Characteristics of included studies and patients are

reported in table 1. We included 26 studies in the meta-analysis (Evans, Akiskal et al. 2005, Kesebir, Vahip et al. 2005, Matsumoto, Akiyama et al. 2005, Benazzi 2006, Karam, Salamoun et al. 2010, Ekinci, Ozdel et al. 2013, Fornaro, Ventriglio et al. 2013, Greenwood, Badner et al. 2013, Kesebir, Gundogar et al. 2013, Mahon, Perez-Rodriguez et al. 2013, de Aguiar Ferreira, Vasconcelos et al. 2014, Eich, Gamma et al. 2014, Harnic, Pompili et al. 2014, Kesebir, Tatlidil Yaylaci et al. 2014, Dolenc, Dernovšek et al. 2015, Innamorati, Rihmer et al. 2015) (Mendlowicz, Akiskal et al. 2005, Mendlowicz, Jean-Louis et al. 2005, Nowakowska, Strong et al. 2005, Vazquez, Kahn et al. 2008, Mazzarini, Pacchiarotti et al. 2009, Nilsson, Jorgensen et al. 2010, Pompili, Innamorati et al. 2014, Russo, Mahon et al. 2014, Rybakowski, Kaminska et al. 2014, Xu, Lu et al. 2014). The included studies contained 5628 subjects, including 2025 with BD, 43 with BPD, 56 with ADHD, 1283 with MDD, 28 with ED, 1757 HC, 436 relatives of patients with BD. Seven studies were carried out in the US or Canada, 6 studies in Italy, 4 in Turkey, and 1 each in Brazil, Slovenia, Switzerland, Lebanon, Japan, Denmark, Poland, Argentina, and China. Most of the included studies included only outpatients (22/26, 84.6%). Twelve studies compared BD vs MDD, 3 studies provided also data about BD-I compared to BD II, 14 studies compared BD vs HC, 8 studies compared MDD vs HC, 16 studies investigated TEMPS scores in BD compared to ADHD, BPD, or ED, 4 studies compared patients with BD vs their relatives, and 4 studies compared relatives of patients with BD vs HC (see table 2 for all references).

TEMPS-A-110, a self-administered version of TEMPS (or no further specified version of the TEMPS-A) questionnaire was used in 14 studies (Evans, Akiskal et al. 2005, Nowakowska, Strong et al. 2005, Benazzi 2006, Ekinci, Ozdel et al. 2013, Fornaro, Ventriglio et al. 2013, Greenwood, Badner et al. 2013, Mahon, Perez-Rodriguez et al. 2013, Eich, Gamma et al. 2014, Harnic, Pompili et al. 2014, Pompili, Innamorati et al. 2014, Russo, Mahon et al. 2014, Rybakowski, Kaminska et al. 2014, Dolenc, Dernovšek et al. 2015, Innamorati, Rihmer et al. 2015). The other 9 studies used the TEMPS – Rio de Janeiro in 1 study (de Aguiar Ferreira, Vasconcelos et al. 2014); TEMPS-A Rome in 1 study (Fornaro, Ventriglio et al. 2013); Lebanese-Arabic TEMPS-A in 1 study (Karam, Salamoun et al. 2010); Turkish version of TEMPS-A in 3 studies (Kesebir, Vahip et al. 2005, Kesebir, Gundogar et al. 2013, Kesebir, Tatlidil Yaylaci et al. 2014); Japanese version of TEMPS-A in 1 study (Matsumoto, Akiyama et al. 2005); Italian version of TEMPS-A in 1 study (Mazzarini, Pacchiarotti et al. 2009); short version of TEMPS-A in 3 studies (Mendlowicz, Akiskal et al. 2005, Mendlowicz, Jean-Louis et al. 2005, Nilsson, Jorgensen et al. 2010); TEMPS-A Buenos Aires in 1 study (Vazquez, Kahn et al. 2008); and the Chinese version of TEMPS-A in 1 study (Xu, Lu et al. 2014).

Detailed information about the study quality is provided in Supplementary e-Table 2.

Comparison of affective temperament scores across diagnostic groups

All results are reported in detail in table 2 and those of particular interest are summarized below.

Bipolar Disorder vs Major Depressive Disorder

The meta-analysis pooled data from 12 studies (n=2204), except for the anxious TEMPS scores, for which only 10 studies provided data (n=1660). Patients with BD had significantly higher cyclothymic (SMD=0.54 [0.38, 0.71], P<0.00001; I^2=65%, P=0.0009), hyperthymic (SMD=0.39 [0.18, 0.60], P=0.0002; I^2=78%, P<0.00001), and irritable (SMD=0.41 [0.22, 0.60], P<0.0001; I^2=73%, p<0.0001) TEMPS scores compared to patients with MDD. Depressive (P=0.29) and anxious (P=0.54) TEMPS scores were not different between the two groups.

Bipolar Disorder Type I vs Bipolar Disorder Type II

The meta-analysis pooled data from 3 studies (n=671), except for anxious TEMPS scores for which only 2 studies provided data (n=443). Depressive TEMPS scores were significantly lower in BD-I compared to BD-II (SMD= -0.25 [-0.41, -0.09], P=0.002; I^2=0%, P=0.61). Cyclothymic (P=0.29), hyperthymic (P=0.12), irritable (P=0.84), anxious (P=0.72) TEMPS scores were not different between BD-I and BD-II.

Bipolar Disorder vs Healthy Controls

The meta-analysis pooled data from 14 studies (n=2452), except for anxious TEMPS scores, for which only 12 studies provided data (n=1928). Cyclothymic (SMD=2.22 [1.61, 2.84], P<0.00001; I^2=97%, P<0.00001), depressive (SMD=1.19 [0.55, 1.82], P=0.0002; I^2=97%, P<0.00001), irritable (SMD=1.29 [0.86, 1.72], P<0.00001; I^2=95%, P<0.00001), and anxious (SMD=1.38 [0.66, 2.09], P=0.0002; I^2=97%, P<0.00001) TEMPS scores were significantly higher in the BD group than in HCs. Conversely, hyperthymic TEMPS scores were significantly lower in the BD group compared to HCs (SMD=-0.44 [-0.74, -0.15], P=0.004; I^2=90%; P<0.00001).

Major Depressive Disorder vs Healthy Controls

The meta-analysis pooled data from 8 studies (n=1901), except for anxious TEMPS score, for

which only 6 studies provided data (n=1344).

Cyclothymic (SMD=0.90 [0.60, 1.20], P<0.00001; I^2=87%, P<0.00001), depressive (SMD=1.29 [0.87, 1.71], P<0.00001; I =93%, P<0.00001), irritable (SMD=0.52 [0.04, 1.00], P=0.03; I^2=95%, P<0.00001), and anxious (SMD=1.01 [0.53, 1.48], P<0.0001; I^2=93%, P<0.00001) TEMPS scores were significantly higher in the MDD group than in HCs. Conversely, hyperthymic TEMPS scores were significantly lower in the MDD group compared to HCs (SMD=-0.68 [-0.85, -0.50], P<0.00001; I^2=61%; P=0.01).

BD vs Psychiatric Disorders Other than MDD

The meta-analysis pooled data from 6 studies (n=262), with 3 studies comparing BD vs ADHD (n=126), 2 studies comparing BD vs BPD (n=80), 1 study comparing BD vs ED (n=56).

Compared to ADHD, the BD group did not differ regarding cyclothymic (p=0.43), hyperthymic (p=0.86), depressive (p=0.79), irritable (p=0.07), or anxious (p=0.40) TEMPS scores.

Compared to BPD, the BD group had significantly higher hyperthymic (SMD=0.69 [0.23, 1.14], P=0.003; I^2=0%, P=0.81) TEMPS scores, and significantly lower depressive (SMD=-1.24 [-1.73, -0.76], P<0.00001; I^2=0%; p=0.67), irritable (SMD=-0.91 [-1.38, -0.45], P=0.0001; I^2=0%, p=0.46), and anxious (SMD=-1.42 [-1.91, -0.92], P<0.00001; I^2= %, P=0.43) TEMPS scores. Conversely, cyclothymic TEMPS scores did not differ between BPD and BD (P=0.19).

Only one study reported data about TEMPS scores in ED, so a subgroup MA was not meaningful.

Finally, subgroup difference analyses showed that MDD, ADHD, BPD and ED differed significantly from BD regarding cyclothymic (p=0.01), hyperthymic (P<0.00001), depressive (P=0.0002), irritable (P<0.00001), and anxious (P<0.0001) TEMPS scores.

BD vs First-degree BD Relatives

Meta-analysis pooled data from 4 studies (n=795). Cyclothymic (SMD=2.89 [1.48-4.29], P<0.0001; I^2=98%, P<0.00001), irritable (SMD=1.90 [0.77, 3.04], P=0.001; I^2=98%, P<0.00001), and anxious (SMD=2.71 [0.23, 5.18], P=0.03; I^2=99%, P<0.00001) TEMPS scores were significantly higher in

the BD group compared to BD relatives. Hyperthymic (P=0.97) and depressive (not significant after the trim and fill procedure; P=0.09 TEMPS scores did not differ between BD and BD relatives.

First-degree BD Relatives vs Healthy Controls

The meta-analysis pooled data from 4 studies (n=1018). Cyclothymic (SMD=1.54 [0.43, 2.65], P=0.007; I^2 = 98%, P<0.00001), irritable (SMD=[0.48, 1.47], P=0.0001 after the trim and fill procedure) and anxious (SMD=2.11 [0.50, 3.72] P=0.01 after the trim and fill procedure) TEMPS scores were significantly higher in BD relatives than in HCs. Hyperthymic (P=0.12) and depressive (P=0.97) TEMPS scores did not differ between BD relatives and HCs.

Heterogeneity and publication bias

No comparison between BD-I and BD-II had an I^2>50%. All comparisons between BD and MDD, BD and HC, MDD and HC, BD vs relatives, and BD relatives vs HC had an I^2>50%.

Begg-Mazumdar Kendall's tau (Begg and Mazumdar 1994), Egger's bias test (Egger, Davey Smith et al. 1997) and the trim and fill method (Duval and Tweedie 2000) did not substantially change the direction and significance of the results in any comparison.

Moderator variables

Results of the meta-regression analyses are reported in table 3. Briefly, in BD vs MDD non-European study origin moderated lower hyperthymic TEMPS scores (N=12, β=-0.44 [-0.82-0.06], R^2=0.28, P=0.02). The moderator effect was confirmed by t-test comparison between the SMD in the BD and MDD groups, according to meta-regression strata (P=0.04) (e-table 3).

In BD vs HC comparisons, male sex in HCs (N=10, β=0.05 [0.01-0.08], R^2=0.00, P=0.01) moderated higher cyclothymic TEMPS scores, but the R^2=0.00 indicated that results were quantitatively irrelevant. Non-European study origin (N=14, β=1.29 [0.12-2.46] R^2=0.18, P=0.03), and male sex in HCs (N=10, β=0.03 [0.005-0.06], R^2=0.16, P=0.02) moderated higher depressive TEMPS scores. Furthermore, non-European study origin moderated higher irritable (N=14, β=1.00 [0.201.81], R^2=0.18, P=0.01) and anxious (N=12, β=1.87 [0.75-3.00], R^2=0.40, P=0.001) TEMPS scores. Higher anxious TEMPS scores were also significantly moderated by male sex in HCs (N=8,

β=0.05 [0.01-0.08], R^2=0.24, p=0.009). The moderator effect of non-European study origin was not confirmed by t-test comparison between SMD in BD and HCs regarding depressive scores (P=0.07), while it was confirmed with irritable (P=0.005) and anxious (P=0.001) TEMPS scores according to meta-regression strata (Supplementary table 3).

In MDD vs HC comparisons, non-European study origin moderated higher cyclothymic (N=8, β=0.56 [0.03-1.14] R^2=0.24, P=0.04) and anxious (n=6, β=0.82 [0.14-1.50], R^2=0.55, P=0.02) TEMPS scores. In MDD vs HC comparisons, active depression compared to euthymia moderated lower irritable (N=5, β=-1.44 [-2.3- -0.6], R^2=0.76, p=0.001), and anxious (N=4, β=-1.03 [-2.02 - -0.04], R^2=0.43, p=0.04) TEMPS scores. Also, male sex in HCs (N=4, β=0.05 [0.02 - 0.07], R^2=0.78, p=0.003) moderated higher anxious scores. The moderator effect of non-European study origin was confirmed by t-test comparison between SMD in MDD and HCs, according to meta-regression strata in cyclothymic (P=0.008) and anxious (P=0.02) scores (Supplementary table 3).

In BD patients vs relatives comparisons, non-European study origin moderated higher anxious TEMPS scores (N=4, β=6.27 [4.74 - 7.81], R^2=0.94, P<0.001), and the effect was confirmed by t-test comparison between SMD in BD patients and relatives according to meta-regression strata (P<0.001) (Supplementary table 3).

In BD relatives vs HC comparisons, non-European study origin moderated lower depressive scores (N=4, β=-2.08 [-3.86 - -0.29], R^2=0.69, p=0.02), and the effect was confirmed by t-test comparison between SMD in BD relatives and HCs according to meta-regression strata (P<0.001) (Supplementary table 3).

Discussion

The results of the first meta-analysis of TEMPS affective scores across mood disorders and pertinent control groups suggest a continuum model of affective temperament domains spanning from HCs through MDD to BD. Cyclothymic and irritable domain score severities appear to

progressively increase according the above mentioned pattern. The same continuum trajectory was observed for cyclothymic, irritable and anxious temperament that each ranged from HCs, through BD relatives, to patients affected by BD, further strengthening the genetic and heritable component as one of the underlying factors that contribute to the multifactorial pathogenesis of BD (Greenwood, Akiskal et al. 2012, Greenwood, Badner et al. 2013). Nonetheless, the above mentioned trend was not replicated with respect to depressive and anxious temperament domains. Conversely, the depressive and anxious domains appear cluster across mood disorders as a group, with similar scores in BD and MDD, which were both significantly higher compared to HCs. A possible interpretation of this finding may be a selection bias, i.e., the inclusion of moderate to severe clinical cases of BD and MDD, rather than of milder presentations. In fact, it has been proposed that higher scores in the cyclothymic, irritable and hyperthymic TEMPS domains correlate significantly with more severe BD presentations (Perugi, Toni et al. 2012), suggesting the possibility of some degree of state dependent effects in the upper severity range in addition to underlying, more stable, trait-dependent temperament ratings.

The finding of higher hyperthymic temperament scores n BD than MDD follow the mood polarity of disorder. However, we also found that HCs had even higher hyperthymic ratings than BD patients. This seeming disconnect is likely due to the fact that BD patients were not always euthymic and that BD more frequent presents with depressive or mixed features than with pure (hypo)mania (Judd, Akiskal et al. 2002, Judd, Akiskal et al. 2003, Judd, Akiskal et al. 2005),s, previously described as the "dark side of hypomania" (Hantouche, Angst et al. 2003, Cassano, Mula et al. 2009). Moreover, patients with atypical depression or BD-II depression appear to have a strong relationship with cyclothymic temperament, whereas BD-I and manic patients have more consistently been related to higher hyperthymic scores. This latter relationship could explain the lower hyperthymic scores in the included BD group compared to HCs, considering that only 4 studies reported separate scores for BD I and BD II.

Pertaining to the continuum model, our results confirm previously hypotheses of increasing

temperamental features across diseases and from diseases through relatives to healthy populations, which is a core feature of an endophenotype (Di Florio, Hamshere et al. 2010). Also, since noncompliance has been recognized as a frequent and core problem in BD management (Levin, Tatsuoka et al. 2015, Sajatovic, Levin et al. 2015), and since cyclothymic temperament has been associated with poor treatment adherence (Fornaro, De Berardis et al. 2013), the cyclothymic TEMPS subscale could possibly be a useful tool in everyday practice, warning about the risk of non-adherence, prompting more careful monitoring, supervision or medication switches from oral to long-acting formulations where available. Even more importantly, cyclothymic temperament is a recognized risk factor for suicidal behavior, being associated with hopelessness beyond polarity in BD. Again, here the cyclothymic TEMPSS subscore could be helpful clinically in increasing surveillance or influencing treatment choice, including lithium (Koek, Yerevanian et al. 2012).

Furthermore, the observed temperamental patterns can at least partially explain similarities and differences within the mood disorder group. Both BD and MDD spend major parts of the illness in the depressive phase (Judd, Akiskal et al. 2002, Judd, Akiskal et al. 2003, Judd, Akiskal et al. 2005), likely relating to the similar depressive temperament ratings. Conversely, our results confirm that, as previously suggested (de Aguiar Ferreira, Vasconcelos et al. 2014) temperament measures are useful in the differential diagnosis between BD and MDD; with significantly higher TEMPS hyperthymic, cyclothymic and irritable domain sores in BD than MDD. Rating these temperamental domains could be useful in particular clinical situations, such as presentation with depressed mood, where distinguishing unipolar from bipolar disorder is key decision factor for treatment decisions, yet, this differentiation can be quite challenging (Hirschfeld 2014).

Regarding the BD vs ADHD comparisons, our results strongly suggest common temperamental features, as indicated before (Landaas, Halmoy et al. 2012), suggesting some shared biological background between the two conditions that are also not infrequently comorbid, especially in youth (Ashcroft, Verdolini et al. 2015, Chen, Chen et al. 2015, Lan, Bai et al. 2015). Moreover, although only two studies reported data about TEMPS-A in BD vs BPD, our preliminary results suggest that

temperament assessments could be helpful in helping to distinguish these two conditions, in addition to taking into consideration a history of childhood sexual abuse, childhood depersonalization, personality variables relating to interpersonal difficulties and sensitivity to criticism, BD family history, and interpersonal features (Bayes, McClure et al. 2015).

Limitations

Results of this study need to be interpreted within its limitations. First, we only investigated TEMPS affective domains, excluding other potentially interesting questionnaires, such as the Tridimensional Cloninger Inventory (Cloninger, Svrakic et al. 1993). However affective domains as measured by TEMPS have consistent biological and genetic correlates (Gonda, Rihmer et al. 2006, Greenwood, Akiskal et al. 2012, Greenwood, Badner et al. 2013), being a fundamental instrument to "look into brain through the mind's lens". Second, included studies did not all use all the same TEMPS version. However, former studies have shown consistent reliability of different TEMPS versions (Vahip, Kesebir et al. 2005) (Akiskal, Akiskal et al. 2005, Krebs, Kazes et al. 2006, Vazquez, Nasetta et al. 2007, Figueira, Caeiro et al. 2008, Borkowska, Rybakowski et al. 2010, Preti, Vellante et al. 2010, Lin, Xu et al. 2013), supporting our choice to pool the results across these different TEMPS versions. Moreover, we accounted for heterogeneity of measurement instruments using random effect model in meta-analysis, and our publication bias and trim and fill analyses confirmed the results. Third, comparisons between BD and ADHD, and between BD and BPD only included 3 and 2 studies, respectively, limiting the validity and generalizability of these results. This sample size limitation is accentuated by the fact that BD, BPD and ADHD have overlapping features and that controversy exists about the appropriate nosological boundaries (Bayes, McClure et al. 2015). Fourth, a deeper insight into the affective temperament can be gained from combining data from different structured questionnaires, such as the TEMPS and TCI. Such analyses have already shown significant correlations between novelty seeking and harm avoidance, on the one hand, and anxious, depressive and cyclothymic temperament domains, on the other (Rozsa, Rihmer et al. 2008). However, such analyses are beyond the aims and scope of this meta-

analysis. Fifth, the vast majority of studies included outpatients, possibly introducing a bias, which, however, was not apparent in our subgroup and moderator analyses. Sixth, not all included studies specified inclusion criteria for first degree-relatives, with two studies (Kesebir, Vahip et al. 2005, Mahon, Perez-Rodriguez et al. 2013) including first degree relatives and siblings, whereas the other two studies did not provide further details about the nature of the familial relationship. We attempted to contact authors, but were unable to obtain clarification, assuming for the purposes of the analyses that the studies included first degree-relatives, in line with the aims of investigating temperament as an endophenotype and as stable trait across families. Finally, while it would be of great interest to assess TEMPS scores in patients with and without a family history of bipolar disorder, this level of detail was unavailable in the meta-analyzed studies, precluding such subgroup analyses.

Despite these limitations, several strengths of this study are also noteworthy. First, to the authors' knowledge, this is the first meta-analysis of studies comparing TEMPS ratings in within and across mood disorders and in comparison to psychiatric controls and HCs. Second, this study identified different patterns of TEMPS scores in different diseases and in comparison to HC. Third, this metaanalysis confirms the continuum pattern of cyclothymic, irritable and anxious temperament, ranging from the lowest scores in HCs, through relatives of patients with BD, to patients affected by MDD and to patients with BD. Fourth, the sample size and the number of studies included in the analyses were robust for most of the analyses and comparisons, at least versus HCs and comparing BD with MDD.

Conclusions

In conclusion, affective temperament as measured by TEMPS has a continuum pattern increasing in severity from HC, through MDD to BD regarding cyclothymic and irritable temperament, from MDD through BD to HC regarding hyperthymic temperament, and from HC through BD relatives to BD regarding cyclothymic, irritable and anxious domains. BD did not differ from MDD regarding depressive and anxious temperament, but these two affective domains separated both

mood disorder from HCs who scored far lower than both MDD and BD. BD did not differ from ADHD in any of the investigated TEMPS domains, suggesting a common biological background, although more data are needed to confirm this. Finally, BPD was associated with higher depressive, anxious, and irritable temperament scores compared to BD, lower hyperthymic scores, but similar cyclothymic scores. However only two studies compared these two populations, underscoring the need for further studies investigating the overlap and differentiating features across severe mental disorders and, especially, BPD and BD.

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Figure 1. PRISMA Flow Diagram of stydy Selection Process.

TABLE1. Main characteristics of included studies reporting TEMPS data in patients with mood disorders.

Study / Country	Design	Inclusion Criteria for Primary Mood Disorder Patients	Inclusion Criteria for Control Group	Exclusion Criteria	Illness Phase BD	Illness Phase MDD	NOS -M	N BD	N BPD	N ADHD	N MDD	N Bulimia or ANBP	N HC	N Relatives
Benazzi 2006 *Italy*	CS outpatients	BD-II, GAF >80	MDD	-	Euthymic	Euthymic	11.00	138..00	-	-	71..00	-	-	-
De Aguiar 2014 *Brazil*	CS outpatients	BD, HAMD>17 and YMRS <8, at least Dep Episode	MDD	-	Euthymic	Euthymic	13.00	90..00	-	-	88..00	-	-	-

Study / Country	Design	Inclusion Criteria for Primary Mood Disorder Patients	Inclusion Criteria for Control Group	Exclusion Criteria	Illness Phase BD	Illness Phase MDD	NOS-M	N BD	N BPD	N ADHD	N MDD	N Bulimia or ANBP	N HC	N Relatives
		with antidepressants for at least 8 weeks												
Dolenc 2015 *Slovenia*	CS outpatients	EuthymicBD	Euthymic, MDD	not stable, not remission for at elast 6 months, psychiatric comorbidity, pregnant women.	Euthymic	Euthymic	13.00	64..00	-	-	36..00	-	-	-
Ecinki 2013 *Turkey*	CS outpatients	>17yo, BD I euthymic HAMD<7 YMRS<5, ADHD, DSM-IV,	ADHD	-	Euthymic	-	16	40	-	40	-	-	40	-
Eich 2014 *Switzerland*	CS out+inpatients	Euthymic BD, DSM-IV, ICD10, Utah	BPD, ADHD	-	Euthymic	-	10	24 (pure 12)	27 (pure 12)	23 (pure 10)	-	-	-	-
Evans 2005 *US, Canda*	CS outpatients	Families with BD I, BD II	HC: No mood disorder, no relatives with mood disorder	-	NA	-	9.00	155..00	-	-	-	-	-	-
Fornaro 2013 *Italy*	CS outpatients	MDD DSMIV, 18-65yo, HAMD>18	HC: no lifetime mood disorder, HAMD <7	lifetime BD, cyclothymia, schizophrenia, psychosis, Axis II or III comorbidity,		Depressed	13	-	-	-	HCL 32 - 182	-	87	-
Greenwood 2013 *US, Canada*	CS outpatients	BD,	MDD, or relatives of patients with BD, or relatives with MDD. HC: SCID ascertained absence of disease	-	NA	-	10.00	177..00	-	-	118..00			
Harnic 2014 *Italy*	CS-outpatients	BD I, II, DSM.IV, Euthymic HDRS <8 YMRS <7, 18-65,	HC	IQ<70, lifetime neurological disease, suicidal ideation,	Euthymic	-	15.00	90..00	-	-	-	-	86..00	-

Study / Country	Design	Inclusion Criteria for Primary Mood Disorder Patients	Inclusion Criteria for Control Group	Exclusion Criteria	Illness Phase BD	Illness Phase MDD	NOS-M	N BD	N BPD	N ADHD	N MDD	N Bulimia or ANBP	N HC	N Relatives
				unstable medical condition, blood exam alterations, substance abuse.										
Innamorati 2015 *Italy*	CS - inpatients	BD-I or II DSM-IV,	MDD	Dementia, delirium	NA	NA	12	206			46	-	-	-
Karam 2010 *Lebanon*	CS outpatients	Non institutionalized adults, meeting CIDI criteria for BD	-MDD, ADHD, HC	-	NA	-	9	18	-	6	64	-	384	-
Kesebir 2005 *Turkey*	CS outpatients	BD I with or without family history for BD	All matched for age, education, gender from a previous study (Vahip et al, 2005) 100 HC matched with patients with BD , 219 first degree relative, and 219 matched with relatives +	-	Euthymic	-	11.00	100..00	-	-	-	-	100 for BD, 219 for Relatives	219
Kesebir 2013 *Turkey*	CS outpatients	MDD DSM-IV, remission,	HC	anxiety, somatoform, alcohol and substance abuse DSM-IV	-	Euthymic	13	-	-	-	100	-	100	-
Kesebir 2014 *Turkey*	CS-outpatients	BD I DSM-IV, remission euthymic HDRS<8, YMRS<5	MDD, HC	Unstable medical condition, condition influencing uric acid, psychiatric comorbidity	Euthymic	Euthymic	14.00	41..00	-	-	30..00	-	43..00	-
Mahon 2013 *US*	CS outpatients	BD I, II, NOS, clinically stable	HC. Unaffected sibling : >2 years older than bipolar	-	Euthymic	-	15.00	55..00	-	-	-	-	109..00	51.00

Study / Country	Design	Inclusion Criteria for Primary Mood Disorder Patients	Inclusion Criteria for Control Group	Exclusion Criteria	Illness Phase BD	Illness Phase MDD	NOS-M	N BD	N BPD	N ADHD	N MDD	N Bulimia or ANBP	N HC	N Relatives
			onset age of patients and at least 25 -											
Matsumoto 2005 *Japan*	CS outpatients	MDD, BD I, BD II, HRSD <10, MRS <12	HC: No psychiatric illness influencing working function, CES-D < 15	Psychotic or organic disorder,	Euthymic	Euthymic	16.00	30..00	-	-	29..00	-	59..00	-
Mazzarini 2009 *Italy*	CS inpatients	BD I, II	MDD	-	NA-	NA	8.00	69..00	-	-	19..00	-	-	-
Mendlowicz 2005 *US*	CS outpatients	Recovered BD I or II (no symptoms or signs 2 months),	HC: normal controls + Relatives of Bipolar Bropands, at least w 2 relatives w BD or BD + either schizoaffective or MDD.	-	Euthymic	-	12.00	23..00	-	-	-	-	102..00	52.00
Mendlowicz 2005b *US*	CS outpatients	Depressed BD I, BD II	MDD	-	Depressed	Depressed	12.00	57..00	-	-	94..00	-	-	-
Nilsson 2010 *Denmark*	CS outpatients	BD, Female, Remission Bipolar (<6 Bech Rafaelsen Mania Scale and <6 Bech Rafaelsen Melancholia Scale)	Only female BPD	Male	Euthymic	-	13	25	31	-	-	-	29	-
Nowakowska 2005 *US*	CS outpatients	BD, euthymic.	MDD euthymic. HC: No history or family history of psychiatric illness, no drugs or Primmedical problems, employed, stable residency	Psychiatric comorbidity, active substance abuse, axis II personality, or eating disorders	Euthymic	Euthymic	13.00	49..00	-	-	25..00	-	47..00	-
Pompili 2014 *Italy*	CS-inpatients	BD, DSM-IV, >18 yo	MDD, DSM-IV -	Neurological disease,	NA	NA	9.00	288(BDII 202.. BDII	-	-	96..00	-	-	-

Study / Country	Design	Inclusion Criteria for Primary Mood Disorder Patients	Inclusion Criteria for Control Group	Exclusion Criteria	Illness Phase BD	Illness Phase MDD	NOS-M	N BD	N BPD	N ADHD	N MDD	N Bulimia or ANBP	N HC	N Relatives
								86)						
Russo 2014 *US*	CS outpatient	BD SCID, Euthymic HDRS <15 CARS-M<8, 18-65	HC: SCID NP negative also for 1 degree relatives, 18-65	Neurological disorder, ADHD, substance abuse 3 months, active medical problem, ECT 12 months	Euthymic	-	14	64	-	-	-	-	109	-
Rybakovsky 2014 *Poland*	CS-outpatients	BD I, BD II, DSM-IV	HC, Bulimia or ANBP	-	NA	-	8.00	28..00	-	-	-	28.00	28..00	-
Vazquez2008 *Argentina*	CS outpatients	First degree relatives of BD patients	HC: Healthy, with no family history of BD	BD, <18 yo		-	15	-	-	-	-	-	115	114
Xu 2014 *China*	PR 2 phases	BD DSM-IV	MDD, and SCL-90, HCL<8, HAM-D < 6, HC	pregnancy, serious general medical illness, history of seizure disorder, DSMIV-TR defined organic mental disorders, dementia, schizophrenia, delusional disorder, schizoaffective disorder, active substance use disorder, and history of mental retardation.	NA	NA	9	228	-	-	285	-	200	-
7 US/Canada, 6 Italy, 4 Turkey, 1 Brazil, 1 Slovenia, 1	3 included inpatients, 22 outpatients, 1 in- and outpatients	23 BD, 1 BD relatives, 2 MDD	13 MDD, 17 HC, 1 ED, 2 BPD, 4 BD relatives, 3 ADHD.	-	BD: 13 euthymic, 1 depressed, others not declared.	MDD: 7 euthymic, 2 depressed, others not declared.	Mean NOS-M =11.46	N BD = 2025	N BPD = 43	N ADHD = 56	N MDD = 1283	N ED = 28	N HC = 1757	N Healthy Relatives = 436

Study / Country	Design	Inclusion Criteria for Primary Mood Disorder Patients	Inclusion Criteria for Control Group	Exclusion Criteria	Illness Phase BD	Illness Phase MDD	NOS -M	N BD	N BPD	N ADHD	N MDD	N Bulimia or ANBP	N HC	N Relatives
Switzerland, 1 Lebanon, 1 Japan, 1 Denmark, 1 Poland, 1 Argentina, 1 China.														

Legend: ADHD: Attention Deficit Hyperactivity Disorder; ANBP: anorexia nervosa bulimic purgative; BD: bipolar disorder; BPD: borderline personality disorder; BPRS: brief psychiatric rating scale; CARS-M: clinician-administered rating scale for mania; CS: cross-sectional; DSM-IV: diagnostic and statistical manual, version IV; GAF: global assessment of functioning; HC: healthy control; HCL: hypomania check-list; HDRS: Hamilton depression rating scale; MDD: major depressive disorder; NOS: New Castle- Ottawa scale-Modified; PR: prospective; SCL-90: symptom check-list 90; YMRS: Young mania rating scale.

Table 2. Comparative meta-analysis of TEMPS score among Bipolar Disorder, Major Depressive Disorder, Attention Deficit and Hyperactivity Disorder, Borderline Personality Disorders, bipolar patients relatives, and healthy controls.

Outcome or Subgroup	Studies	Participants	Heterogeneity	Effect Estimate * (p)	Studies
BD vs MDD					
1.1 Cyclothymic	12	2204	(P = 0.0009); I^2 = 65%	**0.54 [0.38, 0.71] (P < 0.00001)**	Benazzi et al, 2006; DeAguiar et al, 2014; Dolenc et al, 2015; Greenwood et al, 2013; Karam et al, 2010; Kesebir et al, 2014; Matsumoto et al, 2005; Mazzarani et al, 2009; Mendlowicz et al, 2005b; Nowakowska et al, 2005; Pompili et al, 2014; Xu et al 2014.
1.2 Hyperthymic	12	2247	(P < 0.00001);I^2 = 78%	**0.39 [0.18, 0.60] (P = 0.0002)**	
1.3 Depressive	12	2247	(P < 0.00001);I^2 = 78%	-0.11 [-0.31, 0.09] (P = 0.29)	
1.4 Irritable	12	2247	(P < 0.0001); I^2 = 73%	**0.41 [0.22, 0.60] (P < 0.0001)**	
1.5 Anxious	10	1660	(P < 0.0001); I^2 = 79%	-0.08 [-0.32, 0.17] (P = 0.54)	
BD I vs BD II					
Outcome or Subgroup	**Studies**	**Participants**	**Heterogeneity**	**Effect Estimate**	
2.1 Cyclothymic	3	671	(P = 0.21); I^2 = 36%	-0.11 [-0.31, 0.09] (p=0.29)	Evans et al, 2005; Pompili et al, 2014; Xu et al, 2014
2.2 Hyperthymic	3	671	(P = 0.49); I^2 = 0%	0.12 [-0.03, 0.28] (P = 0.12)	
2.3 Depressive	3	671	(P = 0.61); I^2 = 0%	**-0.25 [-0.41, -0.09] (P = 0.002)**	
2.4 Irritable	3	671	(P = 0.34); I^2 = 7%	0.02 [-0.15, 0.18] (p=0.84)	
2.5 Anxious	2	443	(P = 0.40); I^2 = 0%	-0.04 [-0.23, 0.16] (p=0.72)	
BD vs HC					
Outcome or Subgroup	**Studies**	**Participants**	**Eterogeneity**	**Effect Estimate**	Ecinki et al, 2013; Greenwood et al, 2013; Harnic et al, 2014; Karam et al, 2010; Kesebir et al, 2005; Kesebir et al, 2014; Mahon et al, 2013; Matsumoto et al, 2005; Mendlowicz et al, 2005; Nilsson et al, 2010; Nowakowska et al, 2005; Russo et al, 2014; Rybakowsky et al, 2014; Xu et al, 2014.
3.1 Cyclothymic	14	2452	(P < 0.00001); I^2 = 97%	**2.22 [1.61, 2.84] (P < 0.00001)**	
3.2 Hyperthymic	14	2452	(P < 0.00001); I^2 = 90%	**-0.44 [-0.74, -0.15] (P = 0.004)**	
3.3 Depressive	14	2452	(P < 0.00001); I^2 = 97%	**1.19 [0.55, 1.82] (P = 0.0002)**	
3.4 Irritable	14	2452	(P < 0.00001); I^2 = 95%	**1.29 [0.86, 1.72] (P < 0.00001)**	
3.5 Anxious	12	1928	(P < 0.00001); I^2 = 97%	**1.38 [0.66, 2.09] (P = 0.0002)**	

MDD vs HC

Outcome or Subgroup	Studies	Participants	Heterogeneity	Effect Estimate	
4.1 Cyclothymic	8	1901	(P < 0.00001); I² = 87%	**0.90 [0.60, 1.20] (P < 0.00001)**	Fornaro et al, 2013; Greenwood et al, 2013; Karam et al, 2010; Kesebir et al, 2013; Kesebir et al, 2014; Matsumoto et al, 2005; Nowakowska et al, 2005; Xu et al, 2014.
4.2 Hyperthymic	8	1901	(P = 0.01); I² = 61%	**-0.68 [-0.85, -0.50] (P < 0.00001)**	
4.3 Depressive	8	1901	(P < 0.00001); I² = 93%	**1.29 [0.87, 1.71] (P < 0.00001)**	
4.4 Irritable	8	1901	(P < 0.00001); I² = 95%	**0.52 [0.04, 1.00] (P = 0.03)**	
4.5 Anxious	6	1344	(P < 0.00001); I² = 93%	**1.01 [0.53, 1.48] (P < 0.0001)**	

BD vs OTHERS

Outcome or Subgroup	Studies	Participants	Eterogeneity	Effect Estimate	
5.1 Cyclothymic	16	2466	(P = 0.01), I² = 71.6%	**0.31 [0.09, 0.53] (P = 0.006) Subgroup differences (P = 0.01)**	
5.1.1 BD vs MDD	12	2204	(P = 0.0009); I² = 65%	**0.54 [0.38, 0.71] (P < 0.00001)**	
5.1.2 BD vs ADHD	3	126	(P = 0.63); I² = 0%	0.14 [-0.22, 0.50] (P = 0.43)	
5.1.3 BD vs Borderline	2	80	(P = 0.001); I² = 90%	-1.09 [-2.73, 0.55] (P = 0.19)	
5.1.4 BD vs ED	1	56	NA	-0.04 [-0.56, 0.48] (p = 0.88)	
5.2 Hyperthymic	16	2509	(P < 0.00001), I² = 88.7%	**0.30 [0.10, 0.50] (P = 0.004); Subgroup differences (P < 0.00001)**	
5.2.1 BD vs MDD	12	2247	(P < 0.00001); I² = 78%	**0.39 [0.18, 0.60] (P = 0.0002)**	
5.2.2 BD vs ADHD	3	126	(P = 0.91); I² = 0%	-0.03 [-0.39, 0.33] (P = 0.86)	
5.2.3 BD vs Borderline	2	80	(P = 0.81); I² = 0%	**0.69 [0.23, 1.14] (P = 0.003)**	Benazzi et al, 2006; DeAguiar et al, 2014; Dolenc et al, 2015; Greenwood et al, 2013; Karam et al, 2010; Kesebir et al, 2014; Matsumoto et al, 2005; Mazzarani et al, 2009; Mendlowicz et al, 2005b; Nowakowska et al, 2005; Pompili et al, 2014; Xu et al 2014; Ecinki et al, 2013; Eich et al 2014; Nilsson et al, 2010; Rybakowsky et al, 2014.
5.2.4 BD vs ED	1	56	NA	**-0.99 [-1.54, -0.43] (P = 0.0005)**	
5.3 Depressive	16	2509	(P = 0.0002), I² = 84.8%	-0.18 [-0.37, 0.02] (P = 0.08); **Subgroup differences (P = 0.0002)**	
5.3.1 BD vs MDD	12	2247	(P < 0.00001); I² = 77%	**-0.11 [-0.31, 0.09] (p = 0.03)**	
5.3.2 BD vs ADHD	3	126	(P = 0.12); I² = 53%	0.08 [-0.53, 0.69] (p = 0.79)	
5.3.3 BD vs Borderline	2	80	(P = 0.67); I² = 0%	**-1.24 [-1.73, -0.76] (P < 0.00001)**	
5.3.4 BD vs ED	1	56	NA	-0.04 [-0.57, 0.48] (p = 0.88)	
5.4 Irritable	16	2509	(P < 0.00001), I² = 91.3%	0.16 [-0.05, 0.37] (P = 0.14); **Subgroup differences (P < 0.00001)**	
5.4.1 BD vs MDD	12	2247	(P < 0.0001); I² = 73%	**0.41 [0.23, 0.60] (P < 0.0001)**	
5.4.2 BD vs ADHD	3	126	(P = 0.21); I² = 35%	-0.48 [-1.00, 0.03] (p = 0.07)	
5.4.3 BD vs Borderline	2	80	(P = 0.46); I² = 0%	**-0.91 [-1.38, -0.45] (P = 0.0001)**	
5.4.4 BD vs ED	1	56	NA	-0.14 [-0.67, 0.38] (p = 0.59)	
5.5 Anxious	14	1922	(P < 0.0001), I² = 87.0%	-0.24 [-0.48, 0.01] (P = 0.06); **Subgroup differences (P < 0.0001)**	
5.5.1 BD vs MDD	10	1660	(P < 0.00001); I² = 80%	-0.08 [-0.32, 0.17] (P = 0.54)	
5.5.2 BD vs ADHD	3	126	(P = 0.12); I² = 53%	-0.26 [-0.88, 0.35] (P = 0.40)	
5.5.3 BD vs Borderline	2	80	(P = 0.43); I² = 0%	**-1.42 [-1.91, -0.92] (P < 0.00001)**	
5.5.4 BD vs ED	1	56	NA	-0.09 [-0.61, 0.44] (P = 0.74)	

BD vs RELATIVES

Outcome or Subgroup	Studies	Participants	Heterogeneity	Effect Estimate	
6.1 Cyclothymic	4	795	(P < 0.00001); I² = 98%	**2.89 [1.48, 4.29] (P < 0.0001)**	
6.2 Hyperthymic	4	795	(P < 0.00001); I² = 94%	0.01 [-0.65, 0.68] (P = 0.97) 1.16 [0.11, 2.21] (P = 0.03) Not significant after trim and fill.	Greenwood et al, 2013; Kesebir et al, 2005; Mahon et al, 2013; Mendlowicz et al, 2005
6.3 Depressive	4	795	(P < 0.00001); I² = 97%		
6.4 Irritable	4	795	(P < 0.00001); I² = 98%	**1.90 [0.77, 3.04] (P = 0.001)**	
6.5 Anxious	4	795	(P < 0.00001); I² = 99%	**2.71 [0.23, 5.18] (P = 0.03)**	

BD RELATIVES vs HC

Outcome or Subgroup	Studies	Participants	Heterogeneity	Effect Estimate	
7.1 Cyclothymic	4	1018	(P < 0.00001); I² = 98%	**1.54 [0.43, 2.65] (P = 0.007)**	
7.2 Hyperthymic	4	1018	(P < 0.00001); I² = 97%	-0.61 [-1.36, 0.15] (P = 0.12)	
7.3 Depressive	4	1018	(P < 0.00001); I² = 99%	-0.03 [-1.41, 1.35] (P = 0.97)	Greenwood et al, 2013; Kesebir et al, 2005; Mahon et al, 2013; Mendlowicz et al, 2005
7.4 Irritable	4	1018	(P < 0.00001); I² = 97%	**0.67 [-0.10, 1.43] (P = 0.09); 0.98 [0.48, 1.47] p=0.0001 after trim and fill**	
7.5 Anxious	4	1018	(P < 0.00001); I² = 99%	**1.30 [-0.57, 3.17] (P = 0.17); 2.11 [0.50, 3.72] p=0.01 after**	

trim and fill

*Positive effect size indicates higher scores in the former group compared to the latter.

Table 3.Meta-regression of moderators of TEMPS score in mood disorders.

Moderator	Number comparisons	B	95% CI		P value	R^2
		1. BD vs. MDD				
		1.1 Cyclothymic				
Country (Europe [ref] vs. other continents)	12	0.10	-0.24	0.44	0.57	0.00
BD Phase: (Euthymic [ref] vs. depressed)	7	0.13	-0.54	0.80	0.70	0.00
MDD Phase (Euthymic [ref] vs. depressed)	7	0.13	-0.54	0.80	0.70	0.00
Males BD %	10	0.0003	-0.01	0.01	0.96	0.00
Males MDD %	9	-0.010	-0.02	0.005	0.19	0.01
		1.2 Hyperthymic				
Country (Europe [ref] vs. other continents)	**12**	**-0.44**	**-0.82**	**-0.06**	**0.02**	**0.28**
BD Phase: (Euthymic [ref] vs. depressed)	7	-0.41	-1.27	0.44	0.35	0.00
MDD Phase (Euthymic [ref] vs. depressed)	7	-0.41	1.27	0.44	0.35	0.00
Males BD %	10	-0.001	-0.02	0.03	0.91	0.00
Males MDD %	9	-0.009	-0.03	0.01	0.41	0.00
		1.3 Depressive				
Country (Europe [ref] vs. other continents)	12	0.33	-0.08	0.74	0.12	0.03
BD Phase: (Euthymic [ref] vs. depressed)	7	0.15	-0.63	0.94	0.70	0.00
MDD Phase (Euthymic [ref] vs. depressed)	7	0.15	-0.63	0.94	0.70	0.00
Males BD %	11	-0.02	-0.04	0.01	0.06	0.04
Males MDD %	10	-0.003	-0.02	0.02	0.75	0.00
		1.4 Irritable				
Country (Europe [ref] vs. other continents)	12	-0.73	-2.07	0.68	0.28	0.00
BD Phase: (Euthymic [ref] vs.	6	-0.01	-2.60	2.58	0.99	0.00

Moderator	Number comparisons	B	95% CI		P value	R^2
depressed)						
MDD Phase (Euthymic [ref] vs. depressed)	6	-0.01	-2.60	2.58	0.99	0.00
Males BD %	10	0.06	-0.01	0.12	0.11	0.00
Males MDD %	9	0.04	-0.06	0.07	0.91	0.00
		1.5 Anxious				
Country (Europe [ref] vs. other continents)	10	-0.96	-2.00	0.09	0.07	0.00
BD Phase: (Euthymic [ref] vs. depressed)	5	-0.74	-2.67	1.20	0.46	0.00
MDD Phase (Euthymic [ref] vs. depressed)	5	-0.74	-2.67	1.20	0.46	0.00
Males BD %	8	0.03	-0.03	0.08	0.33	0.00
Males MDD %	7	-0.01	-0.06	0.04	0.64	0.00
Males HS		0 studies available				
Males Sib		0 studies available				
Males HC %		2 studies available				
Males BD-I		2 studies available				
Males BD-II		1 studies available				
		2. BD vs. HC				
		2.1 Cyclothymic				
Country (Europe [ref] vs. other continents)	14	1.00	-0.30	2.32	0.13	0.00
BD Phase: (Euthymic [ref] vs. depressed)		All 11 studies euthymic phase				
Males BD %	12	0.03	-0.02	0.07	0.32	0.00
Males HC %	**10**	**0.05**	**0.01**	**0.08**	**0.01**	**0.00**
		2.2 Hyperthymic				
Country (Europe [ref] vs. other continents)	14	-0.33	-0.96	0.31	0.32	0.00
BD Phase: (Euthymic [ref] vs. depressed)	14	0.09	-0.72	0.89	0.84	0.00
Males BD %	12	-0.008	-0.03	0.01	0.52	0.00
Males HC %	10	-0.02	-0.04	0.008	0.20	0.00
		2.3 Depressive				
Country (Europe [ref] vs. other continents)	**14**	**1.29**	**0.12**	**2.46**	**0.03**	**0.18**
BD Phase: (Euthymic [ref] vs.	11	-0.32	-2.02	1.38	0.71	0.00

Moderator	Number comparisons	B	95% CI		P value	R^2
depressed)						
Males BD %	12	0.02	-0.03	0.07	0.42	0.00
Males HC %	**10**	**0.03**	**0.005**	**0.06**	**0.02**	**0.16**
		2.4 Irritable				
Country (Europe [ref] vs. other continents)	**14**	**1.00**	**0.20**	**1.81**	**0.01**	**0.18**
BD Phase: (Euthymic [ref] vs. depressed)	11	-0.48	-1.62	0.65	0.40	0.00
Males BD %	12	0.02	-0.02	0.05	0.35	0.00
Males HC %	10	0.31	-0.002	0.06	0.07	0.00
		2.5 Anxious				
Country (Europe [ref] vs. other continents)	**12**	**1.87**	**0.75**	**3.00**	**0.001**	**0.40**
BD Phase: (Euthymic [ref] vs. depressed)		All 8 studies euthymic				
Males BD %	10	0.03	-0.02	0.08	0.23	0.00
Males HC %	**8**	**0.05**	**0.01**	**0.08**	**0.009**	**0.24**
		3. MDD vs HC				
		3.1 Cyclothymic				
Country (Europe [ref] vs. other continents)	**8**	**0.56**	**0.03**	**1.14**	**0.04**	**0.24**
MDD Phase (Euthymic [ref] vs. depressed)	5	-0.62	-1.59	0.35	0.21	0.00
Males MDD %	5	-0.003	-0.04	0.03	0.99	0.00
Males HC %	6	0.01	-0.02	0.04	0.41	0.12
		3.2 Hyperthymic				
Country (Europe [ref] vs. other continents)	8	0.24	-0.08	0.57	0.15	0.28
MDD Phase (Euthymic [ref] vs. depressed)	5	-0.18	-0.59	0.23	0.39	0.05
Males MDD %	5	-0.002	-0.02	0.02	0.83	0.00
Males HC %	6	0.003	-0.02	0.03	0.76	0.00
		3.3 Depressive				
Country (Europe [ref] vs. other continents)	8	-0.71	-1.51	0.10	0.08	0.18
MDD Phase (Euthymic [ref] vs. depressed)	**5**	**1.65**	**0.82**	**2.47**	**0.0001**	**0.75**
Males BD %	5	0.001	-0.001	0.03	0.32	0.00

Moderator	Number comparisons	B	95% CI		P value	R^2
Males MDD %	5	0.0003	-0.06	0.06	1.00	0.00
Males HC %	6	-0.01	-0.06	0.04	0.58	0.01
		3.4 Irritable				
Country (Europe [ref] vs. other continents)	8	0.74	-0.04	1.52	0.06	0.41
MDD Phase (Euthymic [ref] vs. depressed)	**5**	**-1.44**	**-2.30**	**-0.60**	**0.001**	**0.76**
Males MDD %	5	-0.010	-0.08	0.06	0.79	0.00
Males HC %	6	0.007	-0.06	0.07	0.82	0.03
		3.5 Anxious				
Country (Europe [ref] vs. other continents)	**6**	**0.82**	**0.14**	**1.50**	**0.02**	**0.55**
MDD Phase (Euthymic [ref] vs. depressed)	**4**	**-1.03**	**-2.02**	**-0.04**	**0.04**	**0.43**
Males MDD %			3 studies available			
Males HC %	**4**	**0.05**	**0.02**	**0.07**	**0.003**	**0.78**
		4. BD vs Relatives				
		4.1 Cyclothymic				
Country (Europe [ref] vs. other continents)	4	-0.17	-3.8	3.48	0.93	0.00
BD Phase: (Euthymic [ref] vs. depressed)	4	-2.7	-6.36	0.97	0.15	0.00
Males BD %	3					
Males HS			2 studies available			
Males Sib			1 study available			
		4.2 Hyperthymic				
Country (Europe [ref] vs. other continents)	4	-0.64	-1.96	0.68	0.34	0.25
BD Phase: (Euthymic [ref] vs. depressed)	**4**	**0.98**	**0.09**	**1.87**	**0.03**	**0.68**
Males BD %			3 studies available			
Males HS			2 studies available			
Males Sib			1 study available			
		4.3 Depressive				
Country (Europe [ref] vs. other continents)	4	-2.08	-5.02	0.87	0.17	0.00
BD Phase: (Euthymic [ref] vs. depressed)	4	-1.17	-4.94	2.6	0.54	0.00

Moderator	Number comparisons	B	95% CI		P value	R^2
Males BD %			3 studies available			
Males HS			2 studies available			
Males Sib			1 study available			
		4.4 Irritable				
Country (Europe [ref] vs. other continents)	4	0.34	-2.51	3.19	0.82	0.00
BD Phase: (Euthymic [ref] vs. depressed)	4	-1.65	-4.9	1.59	0.32	0.00
Males BD %			3 studies available			
Males HS			2 studies available			
Males Sib			1 study available			
		4.5 Anxious				
Country (Europe [ref] vs. other continents)	**4**	**6.27**	**4.74**	**7.81**	**P<0.0001**	**0.94**
BD Phase: (Euthymic [ref] vs. depressed)	4	-2.89	-10.37	4.59	0.45	0.00
Males BD %			3 studies available			
Males HS			2 studies available			
Males Sib			1 study available			
		5. BD relatives vs Healthy Controls				
		5.1 Cyclothymic				
Country (Europe [ref] vs. other continents)	4	-1.47	-4.85	1.9	0.39	0.00
Males HS			2 studies available			
Males Sib			1 study available			
Males HC %			2 studies available			
		5.2 Hyperthymic				
Country (Europe [ref] vs. other continents)	4	0.94	0.57	2.45	0.22	0.25
Males HS			2 studies available			
Males Sib			1 study available			
Males HC %			2 studies available			
		5.3 Depressive				
Country (Europe [ref] vs. other continents)	**4**	**-2.08**	**-3.86**	**-0.29**	**0.02**	**0.69**
Males HS			2 studies available			
Males Sib			1 study available			
Males HC %			2 studies available			
		5.4 Irritable				
Country (Europe [ref] vs.			3 studies available			

Moderator	Number comparisons	B	95% CI	P value	R^2
other continents)					
Males HS			3 studies available		
Males Sib			3 studies available		
Males HC %			3 studies available		
		5.5 Anxious			
Country (Europe [ref] vs. other continents)			3 studies available		
Males HS			3 studies available		
Males Sib			3 studies available		
Males HC %			3 studies available		

Highlights

- This is the first meta-analysis of TEMPS score across psychiatric disorders, their relatives, and healthy controls.
- 26 studies, 2,025 patients with BD, 1283 with MDD, 56 with ADHD, 43 with BPD, 436 relatives of BD, and 1757 HCs.
- Cyclothymic ($p<0.001$) and irritable TEMPS scores ($p<0.001$) develop on a continuum, from HCs through MDD to BD.
- Cyclothymic ($p<0.001$), irritable ($p<0.001$) and anxious ($p=0.03$) scores develop on a continuum from HCs, through BD relatives to BD.